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Low serum creatinine and risk of diabetes: The Japan Epidemiology Collaboration on Occupational Health Study

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ABSTRACT

Aims/Introduction: We examined a prospective association between serum creatinine levels and diabetes.

Materials and Methods: The present study included 31,343 male workers without diabetes, and aged between 20 and 64 years at baseline. We calculated the cumulative average of their serum creatinine over the study period. We defined diabetes as either glycated hemoglobin levels ≥6.5%, random glucose levels ≥200 mg/dL, fasting glucose levels ≥126 mg/dL or receiving antidiabetic treatment. Cox proportional hazards regression analysis was carried out to estimate the hazard ratio (HR) and 95% confidence interval (CI).

Results: With a median observation of 7.7 years, 2,509 participants developed diabetes. After adjusting for age, smoking, body mass index, hypertension and dyslipidemia, lower cumulative average serum creatinine levels were related to a greater diabetes risk: HRs were 1.56 (95% CI 1.35–1.82), 1.22 (1.09–1.35) and 1.06 (0.96–1.17) for the participants with serum creatinine <0.70, 0.70–0.79 and 0.80–0.89 mg/dL, respectively, compared with those with 0.90–1.20 mg/dL (*P* for trend <0.001). The serum creatinine-diabetes association was more pronounced among older adults (serum creatinine <0.70 vs 0.90–1.20 mg/dL, HR 1.66, 95% CI 1.37–2.00) than younger adults (HR 1.32, 95% CI 1.02–1.71; *P* for interaction by age group = 0.001).

Conclusions: Low serum creatinine is associated with an increased risk of diabetes. Screening serum creatinine levels can be used to identify those who are at high risk of diabetes.

INTRODUCTION

Skeletal muscle is a primary target for insulin action[1]. Thus, decreased skeletal muscle mass could potentially trigger insulin resistance[2,3], which is an underlying mechanism of diabetes. Two cohort studies from Korea have shown that low muscle mass, defined using relative muscle mass and muscle mass index (appendicular), respectively, is linked with a greater risk of incident diabetes in both young and old people[4,5].

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Creatinine is the only metabolite of creatine phosphate in the skeletal muscle. Under the steady state, it is created at a relatively constant rate by the body depending on the total skeletal muscle mass[6]. Because of the close association between muscle mass and creatinine (correlation coefficient ≥0.7)[7,8], serum creatinine is also used as an inexpensive, easily available surrogate of muscle mass when the kidney functions are stable and protein intake is normal. Thus, it would be interesting to examine a potential association between low serum creatine and the development of diabetes. Three cohort studies from Japan and one from China reported that low serum creatinine was

associated with an elevated risk (hazard ratios [HRs] ranging from 1.4 to 2.0) of diabetes[9–12]. However, these cohort studies had some limitations, including short mean follow-up periods (≤4 years)[9,12], lack of adjustment for potentially important diabetes risk factors (for example, smoking and dyslipidemia)[10,11] or the use of fasting glucose only for diagnosing diabetes[9,11]. Furthermore, all of these studies assessed serum creatinine at baseline only. In addition, no study has examined the creatinine–diabetes association among those with prediabetes, which represents a high risk for diabetes.

Thus, we investigated a prospective association between serum creatinine levels and diabetes risk using repeated measures of creatinine in a male working population in Japan.

METHODS

Study design

We analyzed data from the Japan Epidemiology Collaboration on Occupational Health Study, which is an ongoing cohort study among workers of 12 companies in Japan (study description in the Appendix S1)[13,14]. Briefly, the workers in the participating companies underwent a health checkup every year. They also completed a questionnaire about their medical history and lifestyle. The study protocol, including the consent procedure, was approved by the ethics committee of the National Center for Global Health and Medicine, Japan. In the present study, the 2008 health checkup was considered as the baseline. Two companies had large amounts of missing data in 2008, thus the dataset of 2009 and 2010, respectively, for each company was used as the baseline. We determined the outcome of the present prospective analysis using data of a maximum 8-year follow up from the baseline through March 2017.

Study participants

The present study included only male workers, because the number of women was small (only approximately 100 women had serum creatinine <0.50 mg/dL). Workers were considered initially eligible for the study if they were aged between 20 and 64 years, and had data on serum creatinine at baseline. Of the 38,028 male workers who met the inclusion criteria for participation, we excluded those with diabetes at baseline (n = 2,754), or with missing data on blood glucose (n = 397), glycated hemoglobin (HbA1c; n = 190) or diabetes treatment (n = 154). We further excluded those with a self-reported history of kidney disease (n = 193), hepatitis (n = 186), cardiovascular disease (n = 417) or cancer (n = 239) at baseline to eliminate the influence, if any, of these diseases on serum creatinine. Workers with serum creatinine >1.2 mg/dL, suggestive of renal dysfunction, were also excluded (n = 193)[15]. After further excluding those with missing data on smoking, body mass index (BMI), dyslipidemia and hypertension (n = 388), 32,917 participants remained. We further excluded those who did not attend any subsequent health checkups (n = 1,245) or who attended, but did not receive, glucose measurement (n = 329). Finally, 31,343 participants remained in the analysis.

Exposure

We assessed the levels of serum creatinine using the enzymatic method. To minimize misclassification of exposure, we calculated the cumulative average of serum creatinine from baseline examination up to the start of each follow-up interval. For example, the incidence of diabetes between 2009 and 2010 was related to the average serum creatinine measured at the 2008 and 2009 health checkups, and the incidence of diabetes between 2010 and 2011 was related to the average serum creatinine measured at the 2008, 2009 and 2010 health checkups. The cumulative average of serum creatinine was divided into four categories (<0.7, 0.7–0.79, 0.8–0.89 and 0.9–1.2 mg/dL) according to serum creatinine distribution among participants and with reference to the cut-off points used in previous studies[9–11].

Outcome

Based on the American Diabetes Association criteria, we defined diabetes as either HbA1c levels ≥6.5%, random glucose levels ≥200 mg/dL, fasting glucose levels ≥126 mg/dL or receiving antidiabetic treatment[16]. The participants who met any of the aforementioned conditions during follow up were treated as incident cases of type 2 diabetes.

Covariates

Covariates included baseline age, worksite, smoking, BMI, hypertension and dyslipidemia. We refer to Appendix S1 for the data collection methods, which have been described in previous studies[13,14].

Statistical analysis

Basic characteristics of the present study participants were determined as means (standard deviations) and percentages for continuous and categorical variables, respectively. We tested trend association by carrying out a linear regression analysis for continuous variables and the Cochran–Armitage trend test for categorical variables.

Person-time for each participant was counted by subtracting the date of the baseline survey from the date when incident diabetes was first identified or the date of last health checkup, whichever happened first. We used Cox proportional hazards regression analysis to calculate the HR and 95% confidence interval (CI) for risks of incident diabetes related to cumulative average serum creatinine, which was treated as a time-varying variable. In model 1, we adjusted for worksite and age. Furthermore, we adjusted for BMI, dyslipidemia, smoking and hypertension in model 2. Additionally, we examined the creatinine–diabetes association among the participants with prediabetes at baseline, defined as HbA1c 5.7–6.4% and/or fasting glucose 100–125 mg/dL[16].

Stratified analysis was carried out by the baseline age (<45 or ≥45 years), BMI (<21, 21–24.9 and ≥25 kg/m^2), smoking (yes/no), dyslipidemia status (yes/no) and hypertension status (yes/no), which are associated with both diabetes risk and serum

creatinine levels[17–19]. All of the statistical analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC, USA. Statistical significance was established as two-sided $P < 0.05$.

RESULTS

Table 1 presents participants' characteristics according to the baseline serum creatinine categories. Those with lower serum creatinine were older, tended to be current smokers, and had higher mean high-density lipoprotein cholesterol, blood pressure and fasting glucose.

With a median observation of 7.7 years (range 0.2–9.1 years), 2,509 of the participants developed diabetes. The crude incident rate was 12.3 per 1,000 person-years. As presented in Table 2, worksite- and age-adjusted HR for diabetes among the participants with serum creatinine <0.70 mg/dL was 1.36 (95% CI 1.18–1.58) compared with people with serum creatinine 0.9–1.2 mg/dL (P for trend <0.001). After further adjusting for dyslipidemia, BMI, smoking and hypertension, the association was strengthened (HR 1.56, 95% CI 1.35–1.82). Among the participants with prediabetes at baseline, the multivariable-adjusted HR was 1.45 (95% CI 1.23–1.70) for those with creatinine <0.70 mg/dL compared with serum creatinine 0.90–1.20 mg/dL (P for trend <0.001).

Table 3 presents the association of the cumulative average serum creatinine with diabetes in the stratified analysis. The creatinine–diabetes association was more pronounced among older adults compared with younger adults (P for interaction by age group = 0.001). The serum creatinine–diabetes association did not differ by BMI levels, smoking status, hypertension status or dyslipidemia status (all P for interactions >0.05).

DISCUSSION

Using repeated measurements of serum creatinine, we found that lower levels of cumulative average serum creatinine were associated with an increased risk of diabetes. Similar findings were observed among the participants with prediabetes at baseline. The serum creatinine–diabetes association was more pronounced among the older adults than the younger adults.

The present findings are consistent with those studies using baseline creatinine only[9–12]. In a 4-year follow-up study of Japanese male workers (n = 8,570), the adjusted odds ratio of diabetes was 1.91 for the participants with creatinine 0.40–0.60 mg/dL compared with 0.71–0.80 mg/dL[9]. In another Japanese study of male workers (n = 3,313, with a median observation of 6.7 years), the adjusted HR was 1.9 for the participants with creatinine 0.38–0.69 mg/dL compared with 0.90–1.10 mg/dL[11]. In a study of a general population in Japan (n = 9,667, with a mean observation of 5 years), the adjusted HR was 1.40 for men with creatinine ≤0.7 mg/dL compared with 0.9–1.2 mg/dL, and 1.7 for women with serum creatinine ≤0.5 mg/dL compared with 0.7–1.1 mg/dL[10]. A Chinese study of the general population (n = 57,587, with a mean observation of 3.6 years) also showed that serum creatinine values at baseline were inversely associated with diabetes risk[12]. The present study had a bigger sample (n = 31,343) and longer observation period (median follow-up period of 7.7 years) than previous studies. In addition, we used cumulative average serum creatinine over the study period to minimize the misclassification of exposure. Furthermore, we found low concentrations of serum creatinine were associated with the progression from prediabetes to diabetes, extending the serum creatinine–diabetes association to those with prediabetes. With these methodological advantages and extended findings, the present study provides strong evidence that people with lower serum creatinine are at a greater risk of diabetes.

In the stratified analyses, we observed that the serum creatinine–diabetes association did not differ by BMI or smoking status, which is consistent with previous studies[9,10,12].

Table 1 | Characteristics of participants according to baseline serum creatinine categories

	Serum creatinine (mg/dL)				P for trend
	<0.7	0.7–0.79	0.8–0.89	0.9–1.2	
n	1,492	6,405	10,848	12,598	
Age (years)	44.9 ± 10.4	42.6 ± 10.4	42.1 ± 10.2	43.6 ± 9.7	<0.001
BMI (kg/m^2)	22.9 ± 3.5	23.0 ± 3.3	23.3 ± 3.1	23.7 ± 3.0	<0.001
Current smoker (%)	62.1	52.7	44.5	34.6	<0.001
SBP (mmHg)	123.1 ± 14.5	121.5 ± 14.2	120.6 ± 13.7	120.9 ± 14.0	<0.001
DBP (mmHg)	77.0 ± 10.0	75.8 ± 10.1	75.6 ± 9.9	76.5 ± 10.2	0.07
Hypertension (%)	19.2	15.9	14.6	18.1	0.003
FPG (mg/dL)	97.2 ± 10.2	96.4 ± 9.8	96.2 ± 9.8	96.6 ± 9.6	0.03
HbA1c (%)	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.4	0.02
TG (mg/dL)	128.4 ± 127.1	124.3 ± 100.1	125.8 ± 95.1	130.0 ± 95.7	0.57
HDL-C (mg/dL)	58.0 ± 15.5	57.6 ± 14.7	56.5 ± 14.0	56.3 ± 14.1	<0.001
LDL-C (mg/dL)	114.6 ± 31.7	117.4 ± 30.8	120.0 ± 30.5	123.4 ± 30.3	<0.001
Dyslipidemia (%)	41.3	42.5	44.9	49.0	<0.001

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

Table 2 | Associations between cumulative average serum creatinine and incidence of diabetes

	Cumulative average serum creatinine (mg/dL)				*P* for trend
	<0.7	0.7–<0.8	0.8–<0.9	0.9–1.2	
Overall					
Cases	228	636	832	813	
Person-years	11,599	47,950	73,878	69,866	
Model 1	1.36 (1.18, 1.58)	1.09 (0.98, 1.21)	0.98 (0.89, 1.08)	Reference	<0.001
Model 2	1.56 (1.35, 1.82)	1.22 (1.09, 1.35)	1.06 (0.96, 1.17)	Reference	<0.001
People with prediabetes at baseline					
Cases	198	582	742	745	
Person-years	5,698	21,038	30,377	29,540	
Model 1	1.29 (1.11, 1.52)	1.09 (0.98, 1.22)	0.99 (0.89, 1.10)	Reference	<0.001
Model 2	1.45 (1.23, 1.70)	1.19 (1.06, 1.33)	1.05 (0.95, 1.16)	Reference	<0.001
People with normoglycemia at baseline					
Cases	30	54	90	68	
Person-years	5,900	26,911	43,501	40,325	
Model 1	2.54 (1.64, 3.95)	1.11 (0.77, 1.60)	1.18 (0.86, 1.62)	Reference	0.005
Model 2	2.48 (1.59, 3.89)	1.18 (0.82, 1.68)	1.22 (0.89, 1.68)	Reference	0.003

Model 1: adjusted for age and worksite. Model 2: adjusted for age, worksite, smoking, body mass index, hypertension and dyslipidemia.

Table 3 | Associations between cumulative average serum creatinine and diabetes in subgroups

Subgroup	Cases	Person-years	Cumulative average serum creatinine (mg/dL)				*P* for trend
			<0.7	0.7–<0.8	0.8–<0.9	0.9–1.2	
Age (years)†							
<45	902	122,370	1.32 (1.02, 1.71)	0.95 (0.79 1.14)	0.91 (0.77, 1.06)	Reference	<0.001
≥45	1,607	80,920	1.66 (1.37, 2.00)	1.37 (1.20, 1.57)	1.15 (1.01, 1.30)	Reference	<0.001
	P-interaction = 0.001						
BMI (kg/m^2)†							
<21.0	233	45,210	1.51 (0.94, 2.41)	1.33 (0.91, 1.93)	1.09 (0.75, 1.57)	Reference	0.044
21.0–24.9	1,054	106,383	1.42 (1.12, 1.80)	1.21 (1.03, 1.43)	1.06 (0.91, 1.23)	Reference	<0.001
≥25.0	1,222	51,697	1.64 (1.32, 2.05)	1.19 (1.02, 1.37)	1.05 (0.91, 1.20)	Reference	<0.001
	P-interaction = 0.69						
Smoking‡							
Current	1,212	87,770	1.57 (1.29, 1.91)	1.24 (1.06, 1.45)	0.98 (0.85, 1.15)	Reference	<0.001
Never/former	1,297	115,521	1.47 (1.15, 1.87)	1.17 (1.01, 1.36)	1.11 (0.98, 1.27)	Reference	<0.001
	P-interaction = 0.16						
Hypertension§							
Yes	750	29,299	1.24 (0.93, 1.66)	1.35 (1.12, 1.64)	1.02 (0.85, 1.22)	Reference	0.01
No	1,759	173,992	1.70 (1.42, 2.03)	1.18 (1.03, 1.34)	1.07 (0.96, 1.21)	Reference	<0.001
	P-interaction = 0.48						
Dyslipidemia§							
Yes	1,634	91,162	1.43 (1.18, 1.74)	1.21 (1.06, 1.38)	1.04 (0.92, 1.17)	Reference	<0.001
No	875	112,189	1.72 (1.36, 2.18)	1.22 (1.02, 1.47)	1.09 (0.91, 1.29)	Reference	<0.001
	P-interaction = 0.24						

†Adjusted for age, worksite, smoking, body mass index, hypertension, and dyslipidemia. ‡Adjusted for age, worksite, body mass index, hypertension and dyslipidemia. §Adjusted for age, worksite, smoking, body mass index and dyslipidemia (or hypertension).

Furthermore, we found no effect modification by chronic diseases (for example, hypertension or dyslipidemia). With regard to age, we found that the creatinine–diabetes association was significantly stronger in the older participants (aged 45–64 years) than in the younger adults (aged 20–44 years). In contrast, a small cohort study of Japanese male workers (207 cases of incident diabetes) reported no material differences in the association between serum creatinine and diabetes by age[11]. The present findings based on a much larger number of cases of incident diabetes (n = 2,509) would not only be statistically

reliable, but also reasonable from a mechanistic viewpoint. As creatinine is created proportionally to total skeletal muscle mass[6], low creatinine levels could be an indication of age-associated loss of muscle mass. This aging-related muscle loss has been proposed to increase diabetes risk through several pathways: (i) skeletal muscle tissue is a major target of insulin action, therefore, muscle loss with age results in a diminished target of insulin, and worsens insulin sensitivity and glucose regulation; (ii) aging-related declines in muscle quality can lead to oxidation and inflammation, which cause insulin resistance by inhibiting insulin signal transduction;[20,21] and (iii) fatty infiltration in skeletal muscle that occurs with aging can lead to insulin resistance[22]. Given that aging is also associated with the impairment of β-cell function[23], it is assumed that older adults are more likely to develop diabetes than younger adults in the presence of insulin resistance. If this is the case, older people might benefit more than younger people from strength training, which increases muscle and consequently improves insulin sensitivity. In fact, a study in Japan reported a greater reduction in diabetes risk related to strength training in people aged ≥50 years than their younger counterparts[24]. More studies are required to confirm these findings.

The present study had several strengths, including the large cohort, long-term observation, use of blood glucose and HbA1c for diagnosing diabetes, sufficient cases of diabetes, and annual assessment of serum creatinine. Some limitations also warrant attention. First, serum creatinine was measured in different laboratories in the Japan Epidemiology Collaboration on Occupational Health study. Given that all the laboratories in the present study received high-quality control scores from external agencies, we believe that the measurement is reliable and comparable across participating companies. To further confirm this, we repeated the analysis with data from a big company and found that the adjusted HR was 1.52 (95% CI 1.27–1.81) for men with creatinine <0.70 mg/dL compared with 0.90–1.20 mg/dL, which is similar to the overall analysis. Second, two worksites (approximately 5% of the total study population) did not have disease history data (e.g., kidney disease, hepatitis, cardiovascular disease and cancer) that might have influenced the level of serum creatinine. We confirmed, however, that the results were materially unchanged after excluding people at the two worksites (serum creatinine <0.70 vs 0.90–1.20 mg/dL, adjusted HR 1.56, 95% CI 1.34–1.81). Third, because of the lack of data on potential confounders, such as meat intake, we were unable to control for the potential effects of these factors. Last, the small number of women, especially few (approximately 100) women with serum creatinine <0.50 mg/dL, precluded the assessment of the association between low serum creatinine and diabetes in women.

In conclusion, the present cohort study based on repeated measurements of serum creatinine shows that low serum creatinine is associated with an increased risk of diabetes. Screening serum creatinine levels can be used to identify those at a high risk of diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 | Japan Epidemiology Collaboration on Occupational Health Study design and data collection methods.